

# Evaluation of cardiovascular risk assessment models with respect to the clinical interpretation of atherosclerosis in a different type II diabetes cohort

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## Abstract

Epidemiological studies on cardiovascular risk developed many assessment models which are widely available for the public use. As many arterial occlusive diseases are developed from atherosclerosis in their early stage, it is meaningful to evaluate such models with respect to the clinical interpretation of atherosclerosis so as to promote the preventive care of vascular diseases. Our study aims to make use of the data collection form from the Hong Kong Chinese type II diabetes to evaluate and compare the performance of the risk assessment models of ARIC, FHS, UKPDS using ROC curve.

We found that ARIC's Stroke model gives the best performance whose AUC is 0.646 in model for Black. UKPDS's Stroke has the lowest AUC, 0.497. It was found that ARIC model for the Black Americans has superior performance with respect to the cohort in Hong Kong based on the ROC analysis.

## Introduction

Type II diabetes leads to elevated glucose level and can be complicated to various vascular occlusive diseases, such as atherosclerosis. Since the atherosclerosis is the early stage of cardiovascular diseases (CVD), the identification of atherosclerosis can predict CVD and thus facilitate preventive care of CVD. Although there exist many risk assessment models derived from clinical researches, the models can provide the risk of CVD only but not necessarily indicate the relationship with the diagnosis of atherosclerosis. It is of significant contribution to evaluate and compare the performance of risk assessment models in the detection of atherosclerosis.

Cardiovascular disease (CVD), a group of disorders in the heart and blood vessels, is the leading cause of mortality in people with diabetes, including coronary heart disease (CHD), cerebrovascular disease, peripheral arterial disease, rheumatic heart disease, stroke, congenital heart disease and deep vein thrombosis and pulmonary embolism. Although

there is a higher prevalence of traditional risk factors for CVD (i.e. hypertension, dyslipidemia, obesity) in persons with diabetes than in those without the disorder, these risk factors account for less than half of the mortality from CVD associated with diabetes<sup>1</sup>. Thus, diabetes takes its place alongside the other major risk factors as a strong independent risk factor for CVD. According to some previous research<sup>1,2,3,4</sup>, individuals with diabetes have at least a twofold increased risk for having cardiovascular mortality compared with age-matched subjects without diabetes<sup>5</sup>. Ischemic heart disease and cerebrovascular disease are listed as the important causes of morbidity and approximately 65% of patients with diabetes die from CVD<sup>3,6</sup>.

As the serious consequence of CVD from diabetes is referred above, the risk assessment beneficial to type 2 diabetes appears to be of essential significance. It will have widespread use and is particularly applied for health care planners, industry, providers, insurers and government, as well as clinicians and patients, in order that optimal care can be determined.

## Risk models

Many long-term prospective studies of models for CVD risk have been reported such as ARIC (Atherosclerosis Risk in Communities), FHS (Framingham Heart Study), UKPDS (United Kingdom Prospective Diabetes Study).

The FHS involved 5,209 adults widely aged 30 to 62 at the time of the initial examination since 1948. Participants followed up 12 years, and most attended the 11<sup>th</sup> examination of the original Framingham cohort, and some attended the examination of the Framingham Offspring Study<sup>9,10</sup>. Its risk factors include age, sex, SBP, DBP, Total-C, HDL-C, smoking, diabetes, ECG-LVH (left ventricular hypertrophy by electrocardiography), alcohol and prevalent menopause use (for women)<sup>7,9</sup>. And a conventional criterion was used to diagnose diabetes<sup>13</sup>. The Weibull regression model was applied to be statistical modeling in the study<sup>8</sup>.

UKPDS recruited 5,102 patients with type 2 diabetes from 25 to 65 years old, followed for a median of 10.7 years from 1977. It is a diabetes-specific approach which is advantageous as it has HbA1c as a continuous variable. The UKPDS group replace age by age at diagnosis of diabetes and duration of diabetes as risk factors, besides sex, ethnicity, smoking, SysBP, Total-C, HDL-C, Atrial fibrillation<sup>11</sup>. The study showed that elevated LDL-C is the risk factor most predictive of future CV events<sup>6</sup>. However, the study has the primary limitation that the cohort in the study was selected for a clinical trial, so it is not responsible for the general population<sup>11</sup>.

ARIC was derived from a sizable cohort of 15,792 middle-aged persons (45-64) sampled from four US communities in 1987-1989. It is an engine for general population, with benefit from the remarkable progress in modern biochemistry. This report includes follow-up through 2000 (median, 12.3 years). It contains the risk factors: age, sex, race, smoking, Total-C, HDL-C, SysBP, medication to high blood pressure, diabetes. The study group used Kaplan-Meier-like methods to calculate the relevant probabilities<sup>15</sup>. Unlike the former study of the UKPDS, in which the authors showed that updated mean HbA1c level was more strongly related to increased risk of CVD compared with baseline HbA1c level<sup>14</sup>, the ARIC has only a single HbA1c measurement. The engine may not most truly reflect long-term glycemic control, since hemoglobin A1c is an inherently time-dependent variable. This may conclude that ARIC is likely to underestimate the relationship between HbA1c level and CVD<sup>15</sup>.

However, these models above can not early predict CVD, as they provide only the consequence of the occlusive disease such as atherosclerosis. The previous models all mainly focus on the population of America and Europe, and may not be applied to other populations, such as Chinese people in Asia. If we apply the model directly for Chinese people in Asia, the engine may not reflect the result truly because different ethnic has different value in figures. (i.e. The mean of LDL in Finnish is 4.1, in Chinese is 2.5 mmol/l<sup>16</sup>).

We have not find any risk assessment models which can predict the atherosclerosis so as to support the preventive care of CVD, therefore this study is aimed to make use of the data collection form from the pilot study to evaluate the performance of these risk assessment model using Receiver-Operating Characteristics (ROC)

and compare the models based on the area under the curve (AUC).

## Methods

### *Data Collection*

The risk assessment models were evaluated using the data collected from an ongoing pilot study on the relationship between biomarker profile and hemodynamic effect. The subject recruitment criteria of the pilot study are type II diabetes, age 46-60, Hong Kong Chinese, non-smoking and without any records of stroke and chronic coronary heart disease. Thirty-two subjects (age: mean 54.2, SD 4.5; 10 males and 22 females) were recruited. With the confirmation by a radiologist, the ultrasound images showed the presence of atheromas at the common carotid artery, the internal carotid artery and the bifurcation of eight subjects. No carotid vascular problem was found in the rest of the subjects.

### *Mean Correction*

Each numerical risk factor is adjusted by adding the difference between the mean of that risk factor in the corresponding CVD study,  $m_s$ , and the mean of our collected data,  $m_c$ . The mean-corrected value of risk factor  $x_{mc}$  is calculated using the following formula.

$$x_{mc} = x_c + m_s - m_c$$

where  $x_c$  is the collected datum of risk factor.

### *Risk Assessment Models*

ARIC study provides a web-based engine for analyzing the CHD and stroke risk over a 10-year period based on a number of risk factors whose values can be entered through a graphical user interface in the web (<http://www.aricnews.net/calculator.html>). Since this model considers the ethnic of black or white as one of the risk factors, two sets of the 10<sup>th</sup> year's risk values were generated using the collected data and assuming the ethnics are black and white respectively.

FHS developed a scoring method<sup>17,18,19</sup> to evaluate the 10<sup>th</sup> year risk of Hard Coronary Heart Disease (HCHD), CHD, and Stroke, and 2<sup>nd</sup> year risk of CHD. The values of risk factors are stratified into various levels and mapped to the corresponding points through lookup tables. Adding all these points up results in a total score, which infers the 10-year risk through a lookup table.

UKPDS risk engine focuses on estimating the risk of CVD in type II diabetes. The risk engine is distributed in forms of application software

and MS Excel spreadsheet through its website (<http://www.dtu.ox.ac.uk/riskengine/>). Spreadsheet was used to estimate the risks of fatal and non-fatal stroke and CHD because it can facilitate batch processing of data using the Cox proportional hazards model obtained in the UKPDS.

#### *Performance evaluation*

We envisage the estimated risk as a predictor of carotid atherosclerosis. The gold standard is the radiologist's confirmation of the carotid atherosclerosis plaques in the ultrasound images. The risk and the observation were checked against each other and the Receiver-Operating Characteristics (ROC) curve was plotted to

illustrate the relationship between FPR (x-axis) and TPR (y-axis). The area under the curve (AUC) of the ROC is a positive real number ranging from 0 to 1, which indicates the performance of the risk assessment model. For example, if the AUC is 0, that means all predictions are false. If the AUC is 1, that means all predictions are true. If the AUC is 0.5, that means the predictions are randomly generated. As a result, the risk assessment models can be said to be acceptable only if the AUC is between 0.5 and 1. Based on the value of AUC, the performance of the three risk assessment models can be compared.

Risk Factors	ARIC		FHS				UKPDS
	<i>CHD 10Y</i>	<i>Stroke 10Y</i>	<i>HCHD 10Y</i>	<i>CHD 10Y</i>	<i>CHD 2Y</i>	<i>Stroke 10Y</i>	<i>Fatal and non-fatal CHD and Stroke 10Y</i>
<i>Age</i>	✓	✓	✓	✓	✓	✓	
<i>Age at Diagnosis</i>							✓
<i>Duration</i>							✓
<i>BMI</i>							✓
<i>Sex</i>	✓	✓	✓	✓	✓	✓	✓
<i>Ethnicity</i>	✓	✓					✓
<i>Total-C</i>	✓		✓	✓			✓
<i>Smoker</i>	✓	✓	✓	✓	✓	✓	✓
<i>HDL-C</i>	✓		✓	✓	✓		✓
<i>Sys BP</i>	✓	✓	✓	✓	✓	✓	✓
<i>LDL-C</i>				✓			
<i>Dis BP</i>				✓			
<i>Diabetes</i>	✓	✓		✓	✓	✓	
<i>Alcohol(women)</i>					✓		
<i>Prevalent menopause use</i>					✓		
<i>Medication</i>	✓	✓			✓	✓	
<i>Atrial Fibrillation</i>						✓	✓
<i>HbA1c</i>							✓
<i>CVD</i>						✓	
<i>LVH</i>		✓				✓	
<i>CHD</i>		✓					

Table 1 Overview of risk factors considered in the risk assessment models

### Result

According to the methods above, we put the 32 subjects' data into each model and came to the AUC in Table 2. There is a significantly different AUC among the 3 models. ARIC's Stroke has the best evaluate performance which AUC is about 0.645833 in Black, 0.6409375 in White, while UKPDS's Stroke has the lowest AUC which is around 0.5 (0.497396 for Stroke and 0.515625 for Fatal Stroke). As for the AUC of FHS's CHD and Stroke have a wide rang

from 0.510417 to 0.617188, but most of the indexes are mainly around 0.55. From the average figures of the 3 models AUC, we can see the models' performance directly. We can conclude that ARIC has the best AUC (about 0.6235), and UKPDS has the worst (about 0.5358), which we can say ARIC is the best one among the 3 models to predict CVD in type II diabetes which has great association with carotid atherosclerosis.

Risk	ARIC	FHS	UKPDS
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	<i>CHD</i>	<i>Stroke</i>	<i>CHD</i>	<i>Stroke</i>	<i>CHD</i>	<i>Stroke</i>
<i>AUC</i>	Black 0.609375	Black 0.645833	HCHD 0.617188	Stroke 0.575521	CHD 0.59375	Stroke 0.497396
	White 0.609375	White 0.640625	Lpts CHD 0.510417		Fatal CHD 0.536458	Fatal Stroke 0.515625
			Cpts CHD 0.557292			
			CHD (2Y) 0.557292			
<i>Average AUC</i>	0.6234895		0.563542		0.53580725	

Table 2 Comparison of the performance of the risk assessment models with respect to AUC of ROC

#### Discussion

It has been argued that all patients with diabetes are at high or uncertain risk for CVD and deserve maximal pharmacological vascular protection<sup>16</sup>. Thus, predictors, which may warn diabetic patients with hazard ratio appears to be fairly important in the modern research. However, in the three models, most of the risk factors are conventional ones which can not keep pace with the latest update in the mechanism of atherosclerosis. Novel predominant CVD risk factors are needed to be continually revealed, which may benefit the risk assessment and prognosis and account for a remarkable proportion of cardiovascular diseases in clinical practice. Furthermore, the risk equation in these models is out of flexibility. It may not be updated promptly or has to form a new equation to keep pace with the discovery of novel risk factors. In such case, the lack of flexibility may, in certain extent, prohibit the development of the prediction models, even if new dominant risk factor appears.

This study evaluates the performance of ARIC, FHS and UKPDS models in detecting the atherosclerosis in Hong Kong Chinese type II diabetic patients. It was found that ARIC model for the Black Americans outperforms the other models with respect to a different cohort in Hong Kong based on the accuracy analysis using the ROC.

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